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REVIEW ARTICLE

Harlequin ichthyosis and other autosomal recessive congenital ichthyoses: the underlying genetic defects and pathomechanisms

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Summary

Autosomal recessive congenital ichthyoses (ARCI) include several severe subtypes including harlequin ichthyosis (HI), lamellar ichthyosis and non-bullous congenital ichthyosiform erythroderma. Patients with these severe types of ichthyoses frequently show severe hyperkeratosis and scales over a large part of the body surface from birth and their quality of life is often severely affected. Recently, research into the pathomechanisms of these severe congenital ichthyoses have advanced dramatically and led to the identification of several causative genes and molecules underlying the genetic defects. To date, seven loci have been identified that are associated with ARCI and, among them, five causative genes and molecules have been detected. The five genes are transglutaminase 1 gene (*TGMI*), *ABCA12*, two lipoxygenase genes, *ALOXE3* and *ALOX12B*, and *ichthyin*. One of these components, *ABCA12*, has recently been shown to be a keratinocyte lipid transporter associated with lipid transport in lamellar granules and loss of *ABCA12* function leads to a defective lipid barrier in the stratum corneum, resulting in the HI phenotype. Transglutaminase 1 deficiency was reported to cause a malformed cornified cell envelope leading to a defect in the intercellular lipid layers in the stratum corneum and defective stratum corneum barrier function resulting in an ichthyosis phenotype. Thus, defective intercellular lipid layers are major findings in autosomal recessive congenital ichthyoses. Information concerning ARCI genetic defects and disease pathomechanisms are beneficial for providing better treatments and genetic counseling including prenatal diagnosis for families affected by ichthyoses.

Keywords: *ABCA12*; harlequin ichthyosis; lamellar granules; lamellar ichthyosis; non-bullous congenital ichthyosiform erythroderma; prenatal diagnosis

1. Introduction

Severe autosomal recessive congenital ichthyoses (ARCI) can be devastating to a patients' quality of life in those seriously affected, even though other organs are uninvolved. Harlequin ichthyosis (HI; OMIM #242500), especially, is often fatal in affected newborns [1]. For a long time, the pathomechanisms and underlying genetic defects were unknown, although significant progress has recently been made in the understanding of the molecular basis of human epidermal keratinization processes. Since transglutaminase 1 gene (*TGMI*) mutations were identified as the cause in lamellar ichthyosis (LI) in 1995 [2, 3], mutations in several other genes have also been identified in LI and non-bullous congenital ichthyosiform erythroderma (NBCIE). Mutations in any of the known causative genes can lead to either NBCIE or LI and candidate genes specific to either NBCIE or LI alone have not yet been identified. Based on these facts, it is wise to consider NBCIE and LI as a general blanket diagnosis of covering and range of different disorders with similar and overlapping clinical features [4].

In 2003, *ABCA12* was first reported as the causative gene in type 2 LI (OMIM #601277) [5]. Recently, we have determined *ABCA12* function and clarified the pathomechanisms of *ABCA12* mutations leading to the HI phenotype [6]. *ABCA12* is a keratinocyte transmembrane lipid transporter protein associated with lipid transport in lamellar granules to the surface of granular layer keratinocytes [6]. In addition, several newly recognized molecules have been identified as causes of ARCI. In this article, recent research advances into the pathomechanisms of ARCI including HI and the feasibility of performing DNA-based prenatal diagnoses for ARCI are further discussed.

2. Defective intercellular lipid is the main idea behind the pathomechanisms of autosomal recessive congenital ichthyosis (ARCI)

The underlying genetic defects in ARCI patients, to date, a total of seven loci including candidate genes have been reported as shown in Table 1 [5-13]. The genes responsible in 14q11.2, 2q34, 17p13.1 and 5q33 were identified as *TGMI* [2, 3], *ABCA12* [5, 14], two lipoxygenase genes, *ALOXE3* and *ALOX12B* [15], and *ichthyin* [12], respectively (see Table 1).

Formation of the intercellular lipid layers is essential for epidermal barrier function and defective formation of the lipid layers is thought to result in serious loss of the epidermal barrier function, and to abnormal hyperkeratosis (Fig. 2) [16, 17]. Mutations in the lipid transporter protein, *ABCA12* cause defective lipid secretion into lamellar granules which then become expelled from the apical surface of keratinocytes [6] as mentioned above and lead to either LI [5] and HI [6, 18] phenotypes. Lipoxygenase-3 and 12(R)-lipoxygenase are non-heme iron-containing dioxygenases expressed in the epidermis, and their exact functions are unknown [19, 20]. They may be associated with lipid metabolism in the lamellar granule contents and/or intercellular lipid layers in the epidermis. In addition to HI and LI with defective lipid layers in the stratum corneum as their main pathogenetic mechanism, ichthyosis syndromes are also thought to share similar pathomechanisms. For example, Dorfman-Chanarin syndrome (neutral lipid storage disease) showed malformation of lamellar granules and defective lipid production in lamellar granules caused by a deficiency in the CGI-58 protein that is thought to be involved in the pathogenesis of this form of ichthyosis [21]. In Sjgren-Larsson syndrome harboring fatty aldehyde dehydrogenase (FALDH) gene

(ALDH3A2) mutations, defective lamellar granule formation was reported as one sign of a putative pathogenetic mechanism producing ichthyotic lesions in the patients' skin [22].

Similarly, transglutaminase 1 is an enzyme that was reported to crosslink hydroxyceramide to the cornified cell envelope [23, 24]. Cornified cell envelope formation is essential as the scaffold upon which normal intercellular lipid layer formation in the stratum corneum can then take place [25]. Mutations in the transglutaminase 1 gene (*TGMI*) cause defects in the intercellular lipid layers in the stratum corneum leading to defective barrier function of the stratum corneum resulting in the ichthyosis phenotype seen in LI patients [25] and in transglutaminase 1 knockout mice [26]. It remains to be clarified to what extent a defective cornified cell envelope alone contributes to the barrier abnormality in these conditions. In this context, it is of no doubt that defective formation of the intercellular lipid layers in the stratum corneum due to abnormal keratinocyte lipid metabolism, transport, and/or secretion is a major pathogenetic mechanism in this group of congenital ichthyoses, even if known or as yet undiscovered molecules may also play a significant part in the disease process.

It is certain that transglutaminase 1 is one of the major causative molecules of ARCI [4, 27]. Majority of the cases with *TGMI* mutations show LI phenotype. Most *TGMI* mutations reported in LI families are located in the core domain or upstream of it [4, 27]. *TGMI* mutations were also reported to lead to an NBCIE phenotype in a small number of the families [28-30] and defective transglutaminase 1 is not specific for the classic LI phenotype. We can hypothesize that serious loss of transglutaminase 1

activity might lead to the classic LI phenotype [27] and a partial loss of transglutaminase 1 activity to a mild form of LI [31] or a phenotype of NBCIE [29]. Further accumulation of the ARCI patients with *TGMI* mutations is needed to confirm the correlation between genotype and phenotype in this subgroup of ARCI patients.

Ichthyin is a protein with several transmembrane domains, which belongs to a new family of proteins with an unknown function. Ichthyin-like proteins are localized in the plasma membrane, and share with homologies to both transporters and G-protein coupled receptors [12]. Ichthyin was suggested to be a membrane receptor for certain ligands (trioxilins A3 and B3) from the hepoxilin pathway [12]. However, the exact mechanisms of how *ichthyin* mutations cause an ichthyosis phenotype remain to be clarified.

A large outstanding number of patients with unknown genetic defects still suffer from LI and NBCIE forms. Thus, we cannot exclude the possibility that distinct pathomechanisms not involving abnormal stratum corneum lipid barrier formation underlie such groups of patients. For example, an enhanced serine protease activity was demonstrated as a pathomechanism in the mouse model of Netherton syndrome, one of the major ichthyosis syndromes [32].

From the studies of molecular genetic defects underlying each type of autosomal recessive congenital ichthyosis subtype, the majority of missense mutations in ABCA12 were reported to cause LI phenotype, although one NBCIE case was also reported to harbor ABCA12 missense mutations [5]. Mutations in transglutaminase 1 gene result in phenotypes with both LI [2, 3] and NBCIE [28-30].

Mutations in lipoxygenase-3 and 12(R)-lipoxygenase genes have been reported to lead to both LI and NBCIE phenotypes [15]. Mutations in *ichthyin*, in the majority of patients caused the NBCIE phenotype, however an LI phenotype has been reported in one case [12]. We have clarified that even HI shares the same causative gene, *ABCA12* with type 2 LI [6]. These facts clearly indicate that mutations in any of the known causative genes are not specific to one disease phenotype alone. Thus, based on a comprehensive understanding of the pathophysiology of these diseases, HI, LI and NBCIE can be considered to be a group of distinct but related disorders with overlapping phenotypes.

Until now, no clear genotype/phenotype correlation has been defined for mutations in any of the causative genes leading to the ARCI patient phenotype, except for HI and type 2 LI. Thus, it seems that for *ABCA12* related diseases truncation and/or deletion mutations, at least in one allele, cause an HI phenotype and that a homozygote or a compound heterozygote harboring missense mutations results in LI [5, 6, 18].

3. *ABCA12* deficiency in harlequin ichthyosis and lamellar ichthyosis type 2

Among the severe ARCI, harlequin ichthyosis is the most devastating congenital ichthyosis and affected newborns show large, thick, plate-like scales over the whole body and severe ectropion, eclabium and flattened ears [17]. Type 2 LI is a subtype of LI which links to 2q33-35. Clinically, no distinct characteristic features are known for this type of LI [5, 7, 8]. Mutations in *ABCA12* underlie HI and type 2 LI.

ABCA12 is a member of the large superfamily of the ATP-binding cassette (ABC)

transporters, which bind and hydrolyze ATP to transport various molecules across a limiting membrane or into a vesicle [33]. The ABCA subfamily members are thought to be lipid transporters [34].

Ultrastructurally, lamellar granule abnormalities are apparent in HI patient epidermis [35-38]. The cornified cell envelope appears to be normal in HI and major cornified cell envelope precursor proteins (involucrin, small proline-rich proteins 1 and 2, and loricrin) are normally distributed in the HI epidermis [39, 40]. From these findings, HI and type 2 LI diseases are thought to be caused by a different pathomechanisms from malformations in cornified cell envelope. Several morphologic abnormalities, for example the abnormal lamellar granules in the granular layer keratinocytes and a lack of extracellular lipid lamellae in the stratum corneum, reflect the defective lipid transport via lamellar granules and the malformation of intercellular lipid layers in the stratum corneum in HI [35-39]. In type 2 LI, no distinct ultrastructural features have yet been reported. Abnormal lamellar granules in the granular layer keratinocytes and accumulation of lipid droplets in the stratum corneum, similar findings to that seen in HI, were reported in LI cases without transglutaminase 1 deficiency and some in these LI cases might belong to type 2 LI [41, 42].

The HI patients' epidermis was shown to have defective lipid transport using lamellar granules [6]. In addition, cultured epidermal patient keratinocytes carrying *ABCA12* mutations demonstrated defective glucosylceramide transport but that this phenotype was recoverable by ABCA12 corrective gene transfer [6]. From these findings, we have shed light on the pathomechanisms of HI with *ABCA12* mutations that cause a loss of ABCA12 function. Lack of ABCA12 function subsequently leads to disruption

of lamellar granule lipid transport in the upper keratinizing epidermal cells resulting in malformation of the intercellular lipid layers of the stratum corneum [6]. The fact that ABCA3 (a member of the same protein superfamily as ABCA12) works in pulmonary surfactant lipid secretion again using lamellar granules in lung alveolar type II cells [43] further supports our concept.

Genotype/phenotype correlations with five distinct ABCA12 mutations were reported in nine families of type 2 LI and all five mutations were missense mutations resulting in only one amino acid alteration [5]. In contrast, most mutations in HI are truncation or deletion mutations which lead to severe loss of function of ABCA12 peptide affecting important nucleotide-binding fold domains and/or transmembrane domains. In HI, at least one mutation on each allele must be a truncation or deletion mutation in the conserved region which seriously affects ABCA12 function [6]. Further accumulation of data on ABCA12 mutation protein effects and specific sites is needed to elucidate the genotype/phenotype correlations to aid in predicting HI patients' prognosis once novel combinations of ABCA12 mutations have been identified.

4. DNA-based prenatal diagnosis of severe congenital ichthyoses

ARCI are a group of the most severe genodermatoses and often the patients' quality of life is seriously affected. Thus, the parents' request for prenatal diagnosis is not to be ignored easily. Before the causative genes were identified, prenatal diagnosis had been performed by fetal skin biopsy and electron microscopic observation during the later stages of pregnancies at 19-23 weeks estimated gestational age mainly for HI for more than 20 years [44, 45]. Prenatal diagnosis of LI had been possible by ultrastructural observation of fetal skin samples, although prenatal diagnosis of LI was

the most high risk among the keratinization diseases because LI shows regional, individual, and familial variability in its expression. In the last decade, causative genes for ARCI have been clarified one by one and, as previously described, in 2005, we have identified the underlying gene causing HI [6]. Due to the recent advance in understanding of causative genetic defects for ARCI, it has now become possible to make DNA-based prenatal diagnosis for several ARCI diseases by chorionic villus or amniotic fluid sampling procedures in the earlier stages of pregnancy with a lower risk to fetal health and with a reduced burden on the mothers, as is the case with other severe genetic disorders [46]. In LI families with transglutaminase 1 gene mutations, successful prenatal diagnosis and prenatal exclusion of LI by transglutaminase 1 gene mutation analysis has already been reported [47, 48]. Theoretically, prenatal diagnosis by mutation analysis in lipoyxygenase-3, 12(R)-lipoyxygenase and ABCA12 is available in LI families with previously identified mutations on a case by case basis depending on gene mutations. In the near future, even earlier prenatal detection of ARCI by DNA analysis using fetal cells in maternal peripheral blood circulation [49], and, furthermore, preimplantation genetic diagnosis [50] should be available for ARCI.

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Figure Legends

Figure 1. (a) A newborn patient with HI, harboring ABCA12 mutations. (b) A LI patient with transglutaminase 1 mutations in the neonatal period.

Figure 2. Hypothetical pathomechanisms of ARCI due to ABCA12 and transglutaminase 1 mutations: deficiency of intercellular lipid barrier in the stratum corneum.

(a) Schematic model showing the formation of the normal intercellular lipid layers in the stratum corneum. An intact cornified cell envelope is essential for the correct formation of intercellular lipid layers in the stratum corneum. ABCA12 works in lipid transport via lamellar granules to form an intercellular lipid coat. Transglutaminase 1 (TGase 1) crosslinks the cornified cell envelope precursor proteins.

(b) Schematic model of the malformation of stratum corneum barrier by ABCA12 defects. A loss of ABCA12 lipid transporter function results in abnormal lamellar granules and defective intercellular lipid layers.

(c) Schematic model of the malformation of intercellular lipid layers in the stratum corneum caused by an transglutaminase (TGase 1) enzyme deficiency. Defective cornified cell envelope formation also leads to the collapse of stratum corneum lipid barrier.

Table 1. Causative molecules or loci for ARCI including HI, LI and NBCIE

Molecule	Gene (locus)	Type of Mutations	Phenotype [Reference]	Pathomechanism
ABCA12	<i>ABCA12</i> (2q34)	truncation/deletion/missense	HI [6]	severe deficiency of LG lipid transport
ABCA12	<i>ABCA12</i> (2q34)	missense	LI or NBCIE [5]	mild deficiency of LG lipid transport
transglutaminase 1	<i>TGMI</i> (14q11.2)	missense/deletion/insertion/truncation	LI [2,3] or NBCIE [28, 29]	defective CCE formation
lipoxygenase-3	<i>ALOXE3</i> (17p13.1)	missense/truncation	LI or NBCIE [15]	unknown (abnormal lipid metabolism in keratinocytes?)
12R-lipoxygenase	<i>ALOX12B</i> (17p13.1)	missense/truncation	LI or NBCIE [15]	unknown (abnormal lipid metabolism in keratinocytes?)
ichthyin	<i>ichthyin</i> (5q33)	missense/truncation	NBCIE or LI [12]	unknown
unknown	unknown (3p21)	---	NBCIE [10]	unknown
unknown	unknown (19p12-q12)	---	LI [10]	unknown
unknown	unknown (12p11.2-q13)	---	NBCIE [13]	unknown
unknown	unknown (19p13.2-p13.1)	---	NNCI [9]	unknown

ARCI, autosomal recessive congenital ichthyosis; HI, harlequin ichthyosis; LI, lamellar ichthyosis; NBCIE, non-bullous congenital ichthyosiform erythroderma; NNCI, non-lamellar non-erythrodermic congenital ichthyosis; LG, lamellar granule; CCE, cornified cell envelope



